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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,435	03/20/2001	Kerstin Krieglstein	MBP-005XX	1324

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,435	KRIEGLSTEIN, KERSTIN	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-8 and 11-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-8 and 11-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 19, 2004 has been entered.

2. Applicant's amendment is acknowledged. Claims 1, 5 and 16 have been amended. Claims 2-4 and 9-10 have been cancelled.

3. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejections Maintained

4. The rejection of claims 1, 14-15 and 18 under 35 U.S.C. 102(b) as anticipated by Logan is maintained for the reasons set forth on pages 3-4, paragraph 5 of the previous Office Action.

The rejection was on the grounds that Logan teaches the use of anti-transforming growth factor β (TGF-β) antibodies, Arg-Gly-Asp containing peptides, decorin and its functional equivalents such as biglycan and TGF-β antagonists to prevent, treat or suppress central nervous system pathology. Logan also teaches pharmaceutical compositions containing these agents, which can be administered to

patients to inhibit or enhance the production of extracellular matrix in the central nervous system (see the Abstract).

Since the Office does not have the facilities for examining and comparing applicant's compound with the compound of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the compound of the prior art does not possess the same material structural and functional characteristics of the claimed compound). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that Logan is distinguishable from the presently claimed invention because Logan fails to anticipate requiring a patient having a cerebral disorder that results in damaged neurons. Applicant urges that Logan uses different method steps and is silent in regard to treating predamaged neurons in a manner to prevent neuronal death. Applicant urges that Logan teaches the controlling of scar tissue formation. Applicant urges that Logan is also distinguishable from the claimed method because Logan teaches that the targeting site of administration is extracellular matrix and not predamaged neurons.

Applicant's arguments filed February 19, 2004 have been fully considered but they are not persuasive. It is the Examiner's position that there is nothing on the record to show why the method of the prior art is not the same as the claimed method. The claims are drawn to a method of inhibiting the biological activity of transforming growth factor β on predamaged neurons in cerebral disorders, said method comprising the steps of providing a patient having predamaged neurons and treating said predamaged neurons in said patient with a compound that inhibits the biological activity of transforming growth factor β on said predamaged neurons. Logan teaches methods of for preventing, suppressing or treating a central nervous system pathology

by contacting tissue with an agent (i.e. anti -TGF-β antibodies and TGF-β antagonists) that inhibits TGF-β activity (see the Abstract). Logan teaches that after a penetrating injury of the brain or spinal cord (which include predamaged neurons), there is a failure of axonal growth (page 1). Logan teaches that there are no therapies available to promote successful regeneration and functional reconnection of damaged neural pathways (predamaged neurons) (page 2). Logan also teaches that compositions containing the TGF-β inhibitors can be administered by infusion (i.e. intravenously) (Example 2). Logan teaches a method of administering agents including anti -TGF-β antibodies and TGF-β antagonists) to inhibit the activity of TGF-β in the central nervous system (page 3). In regards to Applicant's assertion that "Logan fails to anticipate requiring a patient having a cerebral disorder that results in damaged neurons", it should be noted that Logan teaches patients that had surgically induced brain lesions (i.e. predamaged neurons) were treated with the TGF-β antagonists of the invention (see Examples II-VIII). In regards to Applicant's assertion that "Logan teaches that the targeting site of administration is extracellular matrix and not predamaged neurons", it should be noted that TGF--β is present particularly after injury has occurred (page 4). Therefore, the TGF-β antagonists or inhibitors are directed to injured tissue. Logan, anticipates the claimed invention.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1 and 14-18 recite the term "predamaged". It is unclear as to what the applicant is referring? Clarification as to the meaning of this term is required.

6. Claims 5-8 and 11-13 recite the phrase "capable of" and the term "substantially". It is unclear as to what the applicant is referring? Clarification as to the meaning of the phrase and term is required.

7. Claim 14 recite the phrase "capable of". It is unclear as to what the applicant is referring? Clarification as to the meaning of the phrase is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1 and 14-18 are rejected under 35 U.S.C. 102(b) as anticipated by Melton et al *(WO 95/10611, published April 20, 1995).*

Claims 1 and 14-18 are drawn to are drawn to a method of inhibiting the biological activity of transforming growth factor β on predamaged neurons in cerebral disorders, said method comprising the steps of providing a patient having predamaged neurons and treating said predamaged neurons in said patient with a compound that inhibits the biological activity of transforming growth factor β on said predamaged neurons.

Melton et al teach a method of inducing neuronal differentiation and preventing the death and/or degeneration of neuronal cells *in vitro* and *in vivo* (page 4). Melton et al teach that the antagonizing agents inhibit the activity of TGF-β (page 4). Melton et al teach that the antagonizing agents (i.e. follistain, a protein containing at least one follistain module and a truncated receptor for a growth factor of the TGF-β family) of the invention can bind to growth factor and sequesters the growth factor such that it cannot bind its receptors (page 4). Melton et al teach that the invention can be used to

treat neurodegenerative disorders including anoxia-ischemia, Alzheimer's disease, Parkinson's disease, neuronal damage resulting from trauma and neural degeneration (page 5). Melton et al also teach that the invention can be used to treat patients with ALS (page 17). Melton et al teach that the antagonizing agents can be administered by many administration routes such as intravenous and oral administration (page 19).

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e.,that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 5-8 and 11-18 are rejected under 35 U.S.C. 103(a) as unpatentable over Logan *(WO 93/19783, published October 14, 1993)* in view of Mattson et al *(Journal of Neurotrama, Volume 11, Number 1, 1994)* and in further view of Alexander et al *(Neurosurgery, 1990, 26/4, p. 559-564, (Abstract only))*.

Claims 1, 5-8 and 11-18 are drawn to a method of inhibiting the biological activity of transforming growth factor β on predamaged neurons in cerebral disorders, said method comprising the steps of providing a patient having predamaged neurons and treating said predamaged neurons in said patient with a compound that inhibits the biological activity of transforming growth factor β on said predamaged neurons and a pharmaceutical composition comprising a first compound capable of substantially inhibiting the biological activity of TGF-β on predamaged neurons caused by cerebral disorders and a second compound for disintegrating blood clots wherein the first and second compound are formulated in a pharmaceutically acceptable carrier.

Logan teaches methods of for preventing, suppressing or treating a central nervous system pathology by contacting tissue with an agent (i.e. anti -TGF-β antibodies and TGF-β antagonists) that inhibits TGF-β activity (see the Abstract). Logan teaches that after a penetrating injury of the brain or spinal cord (which include predamaged neurons), there is a failure of axonal growth (page 1). Logan teaches that there are no therapies available to promote successful regeneration and functional reconnection of damaged neural pathways (predamaged neurons) (page 2). Logan also teach that compositions containing the TGF-β inhibitors can be administered by infusion

(i.e. intravenously) (Example 2). However, Logan teaches a method of administering agents including anti -TGF-β antibodies and TGF-β antagonists) to inhibit the activity of TGF-β in the central nervous system (page 3).

Logan does not teach the use of compound for disintegrating blood clots.

Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Alexandria et al teach that tissue plasminogen activator is effective in lysing blood clots in animals.

Mattson et al teach that neuroprotective factors such as TGF-β are expressed in response to brain injury (see the Abstract). Mattson et al teach that within minutes following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs (page 5).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the urokinse or tissue plasminogen activator of Alexandria et al to the pharmaceutical compositions comprising TGF-β antagonists of Logan used in the method for inhibiting the biological activity of TGF on predamaged neurons in cerebral disorders because Mattson et al teach that within minutes following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs. Therefore, one of skill in the art would be motivated to add the urokinase and plasminogen activator as taught by Alexander et al because Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Additionally, Alexander et al has shown that tissue plasminogen activator is effective in lysing blood clots in animals. It would be

expected barring evidence to the contrary that the addition of urokinase or tissue plasminogen activator would disintegrate blood clots because it is well known in the art that the prevention of blood clots would be necessary for treatment of central nervous systems disorders to stop cerebral hemorrhaging.

10. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
May 26, 2004

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